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The impact on hospital resource utilisation of treatment of hepatic encephalopathy with rifaximin-α: a meta-analysis of data from seven, specialist liver disease treatment centres in the United Kingdom

Short title: Cost effectiveness of rifaximin

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Summary

Background

Rifaximin-α reduces the risk of recurrence of overt hepatic encephalopathy. However, there remain concerns regarding the financial cost of the drug.

Aim

To study the impact of treatment with rifaximin-α on healthcare resource utilisation using data from seven United Kingdom liver treatment centres.

Methods

All seven centres agreed a standardised data set *a priori*. Data characterising clinical, demographic and emergency hospital admissions were collected for the time-periods three, six and 12 months before and following initiation of rifaximin-α. Admission rates and hospital length of stay before and during therapy were compared, and costs of admissions and drug acquisition were estimated using published sources.

Results

Data were available from 326 patients. The mean number of hospital admissions decreased from 2.1 per person per year before rifaximin-α to 1.6 during treatment (p=0.001). The mean hospital length of stay decreased from 13.5 days before, to 8.6 days during rifaximin-α (p=0.017). This resulted in an overall reduction in mean annual bed occupancy from 24.4 days per person before, to 11.5 days during treatment (p<0.001). This translated into a mean reduction in inpatient costs of £6,607 per patient per year. Taking into account drug

costs of £3,379 for one year's treatment with rifaximin-α, there was an estimated annual mean saving of £3,228 per patient.

Conclusions

Initiation of treatment with rifaximin-α was associated with a marked reduction in the number of hospital admissions and hospital length of stay. These data suggest that treatment of patients with rifaximin-α for hepatic encephalopathy was generally cost saving.

Introduction

Hepatic encephalopathy (HE) is a neuropsychiatric complication of liver disease which results from liver dysfunction and/or portosystemic shunting [1]. It spans a spectrum from covert HE—detectable only on neuropsychiatric testing—to overt HE, where clinical features such as confusion, impaired motor function, or decreased conscious level are manifest [2]. Overt HE is estimated to affect 30%—40% of patients with cirrhosis at some time during their disease natural history [3], and it is associated with severely impaired health related quality of life (HRQOL) [4].

The pathophysiology of HE is not fully understood but it is thought that the accumulation of neurotoxins derived from bacteria in the gut, such as ammonia, play a part [5]. For this reason, most treatments for HE target the removal of toxins within the gut, or modify gut microbiota. Non-absorbable disaccharides such as lactulose are recommended as the first line treatment for HE [6] but despite this, recurrence rates of overt HE are high and patient compliance can be poor.

The minimally absorbed antibiotic (0.01%) rifaximin-α has been shown to reduce the risk of recurrence of HE in a high quality randomised controlled trial (RCT), with a hazard ratio of 0.42 compared to placebo [7]. In addition, this trial also showed an improvement in patient HRQOL [8]. Rifaximin has been recommended as second-line therapy as an "add-on" to lactulose after a second episode of overt HE in the recent joint European Association for the Study of the Liver and American Association for the Study of Liver Disease guidelines [6]. However, concerns have been raised about the cost effectiveness of rifaximin [9].

There is emerging evidence to suggest that HE is associated with considerable financial burden to healthcare systems, partly due to high hospital admission rates [10, 11]. Although the

RCT of rifaximin showed a significant reduction in the rate of hospitalisation (hazard ratio 0.50) [7], there are understandable concerns about the reproducibility of such results outside the tightly controlled conditions of a RCT [12]. Real world data, i.e. data derived from routine clinical practice, have the advantage of being potentially more generalisable than some of the results from RCTs.

In this study, we compiled real world data from seven UK liver centres of patients with cirrhosis treated with rifaximin-α for HE. The primary aim was to compare the hospital resource utilisation for patients before and after initiation of treatment with rifaximin, remembering that cirrhosis is a progressive disease with HE carrying the highest mortality of all decompensation events [13].

Methods

Data collection

A standardised data collection *pro-forma* was agreed by all participating centres in advance. Adult patients commenced on rifaximin were identified from the records of the pharmacy department at each specialist hospital centre, and patients who were treated for secondary prevention of overt HE on a background of chronic liver disease were included. Patients with HE due to acute liver failure and patients who had an indication other than HE were excluded. Patient records were reviewed in 2014 and clinical and demographic data were recorded, along with the number and duration of emergency hospital admissions for the periods three, six and 12 months before and after exposure to rifaximin. Other relevant parameters which were collected included disease aetiology, abstinence status and length of abstinence in alcohol-related liver disease (ARLD), time since referral to a hepatologist or gastroenterologist, the presence of a transjugular intrahepatic portosystemic shunt (TIPSS), liver transplant status and mortality. In order to estimate disease severity, Model for End Stage Liver Disease (MELD) was calculated at baseline, at three months and at the end of follow-up. MELD is calculated from serum bilirubin, creatinine and the international normalised ratio (INR) and has been shown to accurately predict three month prognosis following transjugular intrahepatic portosystemic shunt (TIPSS) insertion [14]. More recently MELD has been shown to predict outcome of patients listed for liver transplant and is used for the prioritisation of patients on the active liver transplant list in the US [15] Inclusion of aetiology or complication adds little to the validity of the score [16]. Unlike the Child Pugh score, MELD is independent of the presence and severity of HE [17] and was therefore chosen for use in this study.

Estimation of financial costs

Table 2 shows the sources and values used to estimate costs. Inpatient costs were estimated in UK pounds at 2008/9 prices from published NHS sources at a mean cost of £513 per day for non-elective admissions with liver disease [18]. Rifaximin drug costs were calculated from the price published in the British National Formulary of £259 for 56 550 mg tablets [19], giving an annual drug treatment cost of £3,379 for the licensed HE dose of 550mg twice daily.

Statistical analysis

Whilst admissions data were non-normally distributed, the arithmetic mean value was used to compare these values because we aimed to describe effects at the healthcare system level, rather than at the individual patient level. Mean admission rates and hospital length of stay (HLOS) before and during rifaximin exposure were compared using paired samples t-tests. Otherwise, non-parametrically distributed data were compared using independent-samples Mann Whitney U tests or related-samples Wilcoxon signed rank test. The relationship between disease severity and response to rifaximin were explored using Pearson's correlation between baseline MELD score and HLOS. All statistical analyses were carried out using SPSS version 21.

Results

Three hundred and twenty-six patients were identified across the seven centres. 169 patients (51.8%) were prescribed rifaximin at a dose of 550mg twice daily, 151 (46.3%) were prescribed 400mg twice daily and six (1.8%) were taking another dose. The patient characteristics are summarised in Table 1. The most common liver disease aetiology was ARLD, affecting 199 patients (61%), 20 of whom also had another aetiology recorded (HCV, 12 patients; HBV, two; non-alcoholic fatty liver disease (NAFLD), four; haemochromatosis, two patients). Non-alcoholic steatohepatitis (NASH) and infection with hepatitis C virus (HCV) accounted for 15% and 13% of patients, respectively. Ten patients had hepatocellular carcinoma. Mean age was 59 (S.D. 12) years and 225 (69%) were male. 282 patients (87%) were prescribed concurrent lactulose. In terms of disease severity, mean MELD score was 15.1 (S.D. 5.8) and Child Pugh grades were as follows: A, 29 (9%); B: 141 (43%); and C, 124 (38%). 33 patients (10%) had a TIPSS placed prior to the initiation of exposure to rifaximin, 12 of which were placed within six months of rifaximin treatment initiation.

Of the patients with ARLD, 115 (58%) were abstinent from alcohol when rifaximin was initiated, 64 (32%) were actively drinking alcohol, and in 22 (11%) the alcohol status was unclear. Of the patients who abstained from alcohol, 69 (60%) had been abstinent for more one year, 24 (21%) for six to 12 months, whilst 20 (17%) had been abstinent for less than six months.

The time interval between referral to a liver specialist and commencement of rifaximin was less than three months in 37 patients (11%), three to six months in 24 (7%), six months to one year in 26 (8%) and more than one year in 169 patients (52%). Time since referral was unclear in 70 patients (21%).

The outcomes of all patients are illustrated in figure one. 69 patients (21%) died within one year of rifaximin treatment initiation. The 30 day, 90 and 180 day mortality rates were 6%, 11% and 17%, respectively. Median baseline MELD score was higher in the patients who died (17.6, IQR 8.7) compared with those who remained alive and had not been transplanted at one year (12.6, IQR 5.6; $p<0.001$). There were 45 patients (14%) who underwent liver transplantation within one year of treatment initiation with rifaximin, with a median baseline MELD of 17.4 (IQR 6.4). Rifaximin was discontinued in 31 (10%) patients; in five this was because no improvement in clinical condition was observed, in 11 the liver function had improved substantially, or HE was felt to have resolved. Two patients reported adverse events (nausea in one and not recorded in the other) and five were non-compliant. There were no reported cases of Clostridium difficile infection.

Of the remaining 181 patients, complete data covering all study periods (3, 6 and 12 months before and after rifaximin exposure) were available for 141 patients (78%). Figure 2 illustrates the pattern of admissions and hospital length of stay (HLOS) over all periods, showing that admissions increased over the year prior to rifaximin with the greatest number and longest HLOS occurring during the three months prior to rifaximin initiation (mean 0.35 admissions and 4.47 days per month). During rifaximin treatment, hospital admissions decreased, with a progressive reduction in the HLOS throughout the year from 2.14 days per month in the year prior, to 1.02 days per month ($p<0.001$) in the year following rifaximin treatment initiation.

There were complete, paired, 12 monthly data before and after rifaximin exposure available for 158 (87%) of the patients who remained alive and had not undergone liver transplantation. This showed a significant reduction in the mean number of emergency

hospital admissions from 2.1 (SD 2.4) admissions before to 1.6 (SD 2.0) during rifaximin treatment (p=0.001). The mean HLOS per admission reduced from 13.5 (SD 15.9) days before to 8.6 (SD 11.5) days during rifaximin treatment (p=0.017). This amounted to an overall reduction in the mean annual HLOS from 24.4 (SD 29.7) days per year, to 11.5 (SD 18.6) days per year following initiation of rifaximin (p<0.001).

Estimated inpatient costs, using published NHS reference prices, showed that mean annual emergency inpatient admission costs were reduced from £12,522 per year prior to rifaximin initiation, to £5,915 per year following rifaximin treatment initiation, an annual saving of £6,607, without accounting for the drug acquisition cost. Including the drug cost of one year's treatment with rifaximin (£3,379), resulted in a mean saving of £3,228 per patient per year (Figure 3).

Comparing disease severity data from patients with a MELD score available at both baseline and at three months (70—110 days) after treatment initiation with rifaximin (n=118), there was no change from median MELD score at baseline (14.0, IQR 6.3) to three months (13.4, IQR 6.5, p=0.309). Similarly, in patients with MELD data at baseline and one year (274—456 days; n=109) there was no significant change from median MELD at baseline (11.6, IQR 4.8) to one year (11.8, IQR 5.4; p=0.150).

There was no correlation between baseline MELD and the reduction in emergency hospital admissions (Pearson correlation=0.025; p=0.747). There was no statistically significant difference in the change in HLOS comparing patients with previous TIPSS to those without (mean annual reduction in HLOS 13.3 (SD 29.3) days vs 9.6 (SD 11.5) days, p=0.305). No difference was observed between the median reduction in HLOS of patients under the care

of a liver specialist for less than three months and those treated for more than three months (12.0, IQR 42.8 days vs 7.0, IQR 22.0 days, p=0.491).

Of patients with ARLD, those who were actively drinking alcohol at baseline had a more pronounced reduction in their median annual HLOS at 19.0 days (IQR 44.0) than did those who were abstinent, at 9.0 days (IQR 19.0) which was nearing significance at the conventional level of significance (p=0.052). However, the reduction in annual HLOS was similar between those patients who achieved abstinence and those who continued drinking during the one year follow up (20.0 days (IQR 36.0) vs 23.5 days (IQR 49.8; p=0.934). Given the potential impact of active alcohol consumption on the likelihood of being admitted to hospital, the 12 month data was analysed excluding the ARLD patients who were not abstinent at baseline. This showed a reduction in the mean admission number from 1.9 (SD 1.9) to 1.4 (SD 2.3) days (p=0.003), and annual HLOS reduced from 19.9 (SD 26.4) days before rifaximin to 9.6 (SD 16.7) days after (p<0.001).

Discussion

This observational study characterised data from seven large, UK hospitals, representative of the spectrum of liver centres from district general hospitals, to tertiary and liver transplant units. We investigated the impact of treatment with rifaximin on hospital resource utilisation in patients with HE on a background of cirrhosis. We used a before and after design, effectively allowing patients to be used as their own controls with standardised datasets collected from the seven UK centres. We believed that for a progressive disease such as advanced liver disease that this would provide a conservative picture of any resulting change, given that we would expect there to be a natural increase in resource utilisation resulting from a progressive deterioration in clinical condition.

There is good evidence for the efficacy of rifaximin as second-line treatment in HE, in particular in combination with lactulose [7]. However, there remain reservations about the cost effectiveness of the drug and there has been a reluctance to approve its use in some countries [9]. Given the high level of resource utilisation associated with HE and, in particular, high inpatient costs, we aimed to investigate the impact of rifaximin on this specific cost of care. Overall we found a 35% reduction in the mean number of annual emergency inpatient admissions (2.1 to 1.6 admissions), and a 53% reduction in mean annual bed occupancy (24.4 to 11.5 days) due to the combined impact on resource use of a reduction in hospital admissions, and a further saving from a reduction in hospital length of stay when patients were actually admitted.

We considered a number of potential study limitations. One of these, alcohol consumption, was thought to potentially play an important role. Patients who were actively drinking alcohol at baseline had a more pronounced reduction in admissions following rifaximin

exposure. Interestingly, this effect was not confined to patients who subsequently became abstinent but was also evident in those patients who continued to drink alcohol during the period of follow-up. One explanation for this could be that, even in active drinkers, alcohol intake was considerably reduced during follow-up resulting in a degree of re-compensation of liver function and/or fewer alcohol-related admissions, such as alcohol withdrawal. Separate analysis of admissions data following exclusion of those with ARLD who continued drinking alcohol showed that the HLOS was reduced for these patients, both before (19.8 days) and during rifaximin (9.6 days) but the overall percentage reduction in resource use remained similar at 52%. The length of time patients had been under the care of a liver specialist (gastroenterologist or hepatologist) was also examined to determine if patients who had been recently referred had other aspects of their care optimised, alongside the commencement of rifaximin. However, we found no difference comparing patients who had been under the care of a specialist for less than three months with those attending a specialist for a longer time period. Liver disease severity, as measured by MELD score, was also investigated. There was no change from baseline MELD to MELD at either three months or one year. In addition, there was no correlation observed between baseline MELD and HLOS, suggesting that disease severity alone was not associated with a treatment response to rifaximin.

In terms of published data on this matter, to our knowledge there is one other study which considered the impact of rifaximin on healthcare resource utilisation but it had a number of limitations [20]. All patients had been taking lactulose for six months or more for HE and were then switched to rifaximin when the drug became available in the United States. The cohort studied did not therefore accurately reflect what is now standard clinical practice where

rifaximin is reserved for patients with recurrent overt HE and where it will be prescribed in addition to, not instead of, lactulose.

By contrast, our study included patients who were representative of current evidence-based practice. The majority (87%) of patients were prescribed concurrent lactulose, similar to the 91% in the previous RCT [7], and standard practice across all seven centres was for rifaximin to be used as a second line therapy. Another strength of our study was the multicentre nature of the study that included seven specialist liver centres (two liver transplant centres, three tertiary liver centres and two large district general hospitals) meaning that the results should be generalisable across clinical practice elsewhere.

Retrospective studies can suffer from incomplete data. While we had some missing values, particularly in situations where admission data could not be accurately collected because patients were admitted to other hospitals, data covering the 12 months before and during rifaximin was available for 87% of the patients, thus providing a large and reasonably complete dataset. One potential criticism of our study design could be that all emergency admissions were included, rather than only those relating to HE related admissions. We chose this approach because pilot work had demonstrated that patients admitted for other, ostensibly unrelated reasons (e.g. limb fracture) turned out to have HE as a likely contributing factor upon case-note review. There is also the possibility that rifaximin has additional beneficial effects beyond control of HE, for example in reduction of portal hypertension [21] or prevention of spontaneous bacterial peritonitis [22], therefore it was felt that inclusion of all emergency admissions was most appropriate. In addition, HE was not a diagnostic code within the ICD-10 classification (the coding system used in all NHS hospitals) meaning that HE related admissions were likely to be underestimated. By excluding elective

admissions, frequent events such as hospital admissions for uncomplicated, large volume paracentesis did not contribute. We recognised that some, non-HE related emergency admissions may have been included, but this was thought to be constant both before and during rifaximin exposure.

In conclusion, this study that characterised real world data from seven UK specialist liver centres demonstrated that treatment with rifaximin to reduce the frequency of overt HE in those with advanced liver disease was associated with a large reduction in hospital admissions and a reduction in length of stay even when hospital admission was required. Before rifaximin treatment mean annual HLOS was high, consistent with previous reports of healthcare resource utilisation [11, 23, 24]. Following initiation with rifaximin treatment, annual HLOS fell by more than 50% resulting in a mean saving of £6,607 per patient per year in hospital admission costs in our cohort. After accounting for drug acquisition costs there remained a substantial financial saving of approximately £3,000 per patient per year.

Table 1 | Baseline characteristics of included patients*.

	Royal Bolton Hospital	Bristol Royal Infirmary	Ninewells Hospital, Dundee	The Royal Liverpool Hospital	King's College London	Freeman Hospital, Newcastle	Queen Alexandra Hospital, Portsmouth	All centres
Patients (n)	30	45	25	49	78	64	35	**326**
Age (years)	60.5 (11.2)	59.8 (12.3)	57.7 (13.1)	55.3 (13.1)	56.9 (12.1)	61.4 (9.5)	58.3 (11.4)	**58.5 (11.8)**
Males (n, %)	18 (60.0%)	31 (68.8%)	17 (68.0%)	38 (77.5%)	55 (70.5%)	46 (71.9%)	20 (57.1%)	**225 (69.0%)**
TIPSS (n, %)	0 (0.0%)	4 (8.9%)	9 (36.0%)	1 (2.0%)	10 (12.8%)	6 (9.4%)	5 (14.3%)	**35 (10.7%)**
Concurrent lactulose	30 (100.0%)	40 (88.9%)	25 (100.0%)	49 (100.0%)	55 (70.5%)	53 (82.8%)	29 (82.9%)	**282 (86.5%)**
Aetiology*								
ARLD	25 (83.3%)	29 (64.4%)	13 (52.0%)	29 (59.2%)	42 (53.8%)	39 (60.9%)	22 (62.9%)	**199 (61.0%)**
NASH	3 (10.0%)	7 (15.6%)	9 (36.0%)	5 (10.2%)	7 (9.0%)	12 (18.8%)	6 (17.1%)	**49 (15.0%)**
HBV	0 (0.0%)	1 (2.2%)	0 (0.0%)	1 (2.0%)	1 (1.3%)	1 (1.6%)	0 (0.0%)	**4 (1.2%)**
HCV	3 (10.0%)	4 (8.9%)	3 (12.0)	11 (22.4%)	10 (12.8%)	8 (12.5%)	4 (11.4%)	**43 (13.2%)**
AIH/PBC/PSC	0 (0.0%)	3 (6.7%)	1 (4.0%)	3 (6.1%)	10 (12.8%)	1 (1.6%)	4 (11.4%)	**22 (6.7%)**
Cryptogenic	0 (0.0%)	1 (2.2%)	0 (0.0%)	3 (6.1%)	4 (5.1%)	4 (6.3%)	0 (0.0%)	**12 (3.7%)**
Miscellaneous	0 (0.0%)	1 (2.2%)	2 (8.0%)	2 (4.1%)	9 (11.5%)	2 (3.1%)	1 (2.9%)	**17 (5.2%)**
Baseline MELD: mean (SD)	17.5 (5.6)	14.3 (4.6)	15.3 (5.2)	12.8 (4.6)	16.6 (6.9)	12.9 (3.7)	17.9 (6.9)	**15.1 (5.8)**
≤10	1 (3.3%)	10 (22.2%)	3 (12.0%)	13 (26.5%)	8 (10.3%)	10 (15.6%)	4 (11.4%)	**49 (15.0%)**
10-15	11 (36.7%)	18 (40.0%)	9 (36.0%)	21 (42.9%)	32 (41.0%)	36 (56.3%)	12 (34.3%)	**139 (42.6%)**
15-25	15 (50.0%)	15 (33.3%)	11 (44.0%)	15 (30.6%)	26 (33.3%)	17 (26.6%)	15 (42.9%)	**114 (35.0%)**
≥25	3 (10.0%)	0 (0.0%)	1 (4.0%)	0 (0.0%)	11 (14.1%)	0 (0.0%)	4 (11.4%)	**19 (5.8%)**
Unknown	0 (0.0%)	2 (4.4%)	1 (4.0%)	0 (0.0%)	1 (1.3%)	1 (1.6%)	0 (0.0%	**5 (1.5%)**
Baseline Child Pugh class								
A	TO	1 (2.2%)	2 (8.0%)	9 (18.4%)	5 (6.4%)	9 (14.1%)	3 (8.6%)	**29 (8.9%)**
B	BE	16 (35.6%)	14 (56.0%)	24 (49.0%)	39 (50.0%)	37 (57.8%)	11 (31.4%)	**141 (43.2%)**
C	ADDED	26 (57.8%)	9 (36.0%)	16 (32.7%)	34 (43.6%)	18 (28.1%)	21 (60.0%)	**124 (38.0%)**
Unknown		2 (4.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	**32 (9.8%)**

*Some patients had more than one liver disease aetiology.

Table 2 | Cost estimates: sources and values

Cost	**Source**	**Value**
Rifaximin drug cost	British National Formulary August 2015 [19]	56 x 550 mg tablets = £259.23 1 year treatment of 550mg twice daily = £3,379.25
Cost of emergency admission with liver disease	NHS reference costs 2013 to 2014 [18] Liver Failure Disorders without Interventions, with CC Score 0-4: Non-elective inpatients short-stay	Unit cost £513/day

Figure 1 | Outcomes at one-year post initiation of treatment with rifaximin-α.

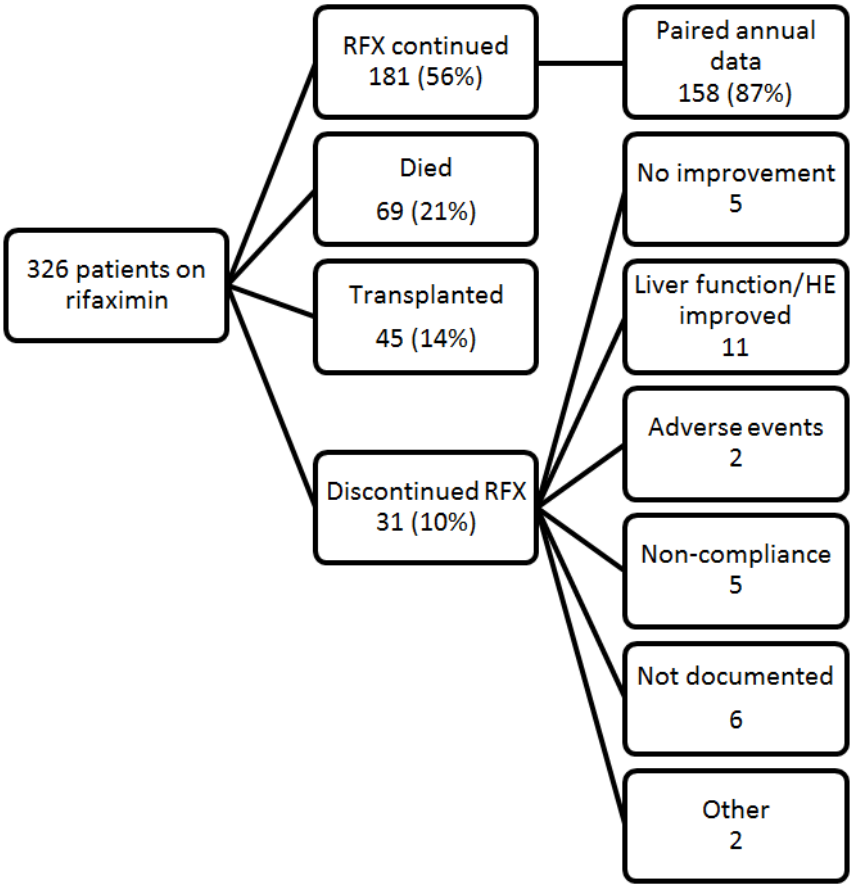
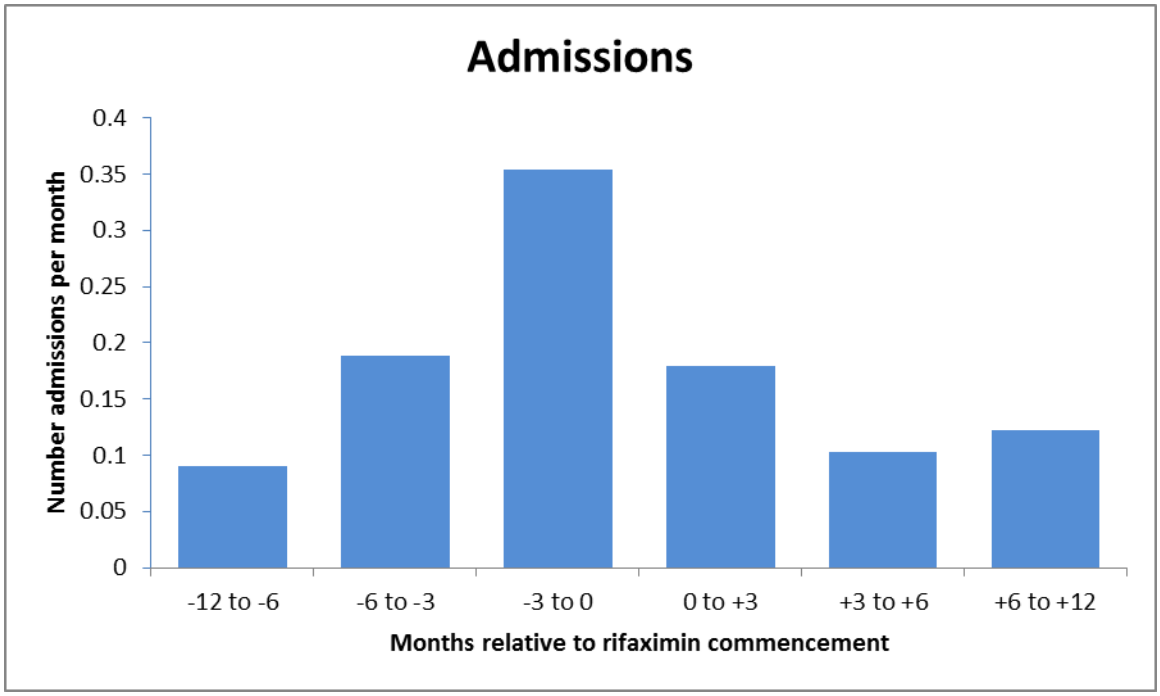


Figure 2 | Pattern of mean number of admissions (A) and mean length of emergency hospital admissions (B) during study period

A



B

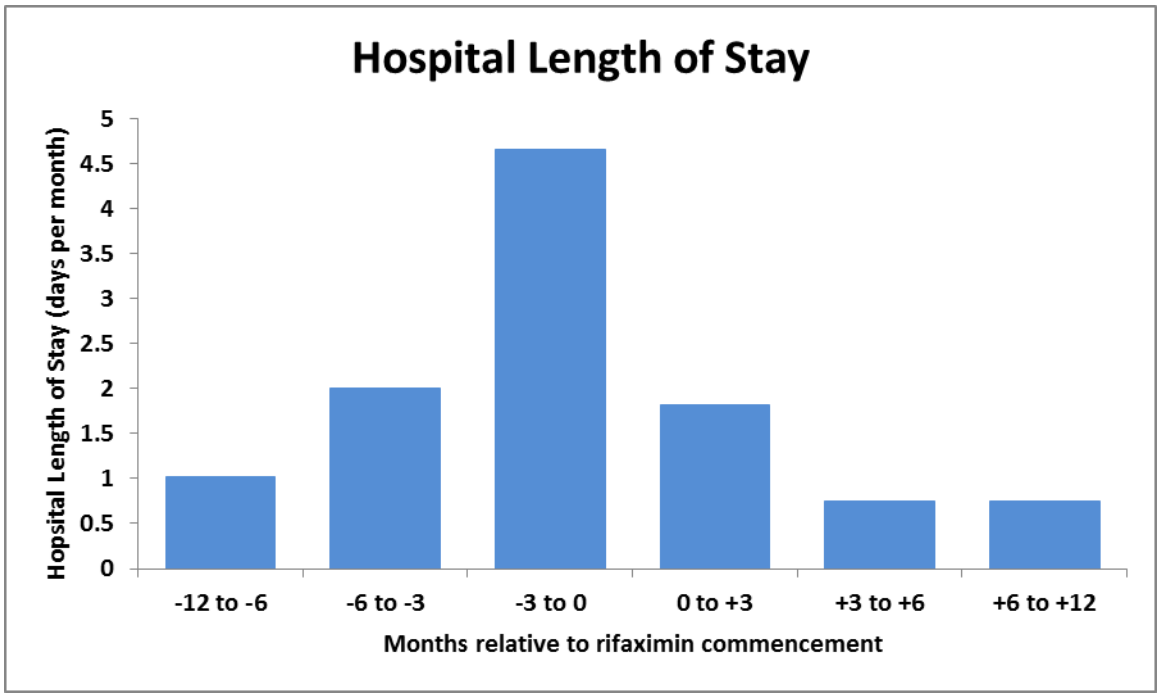
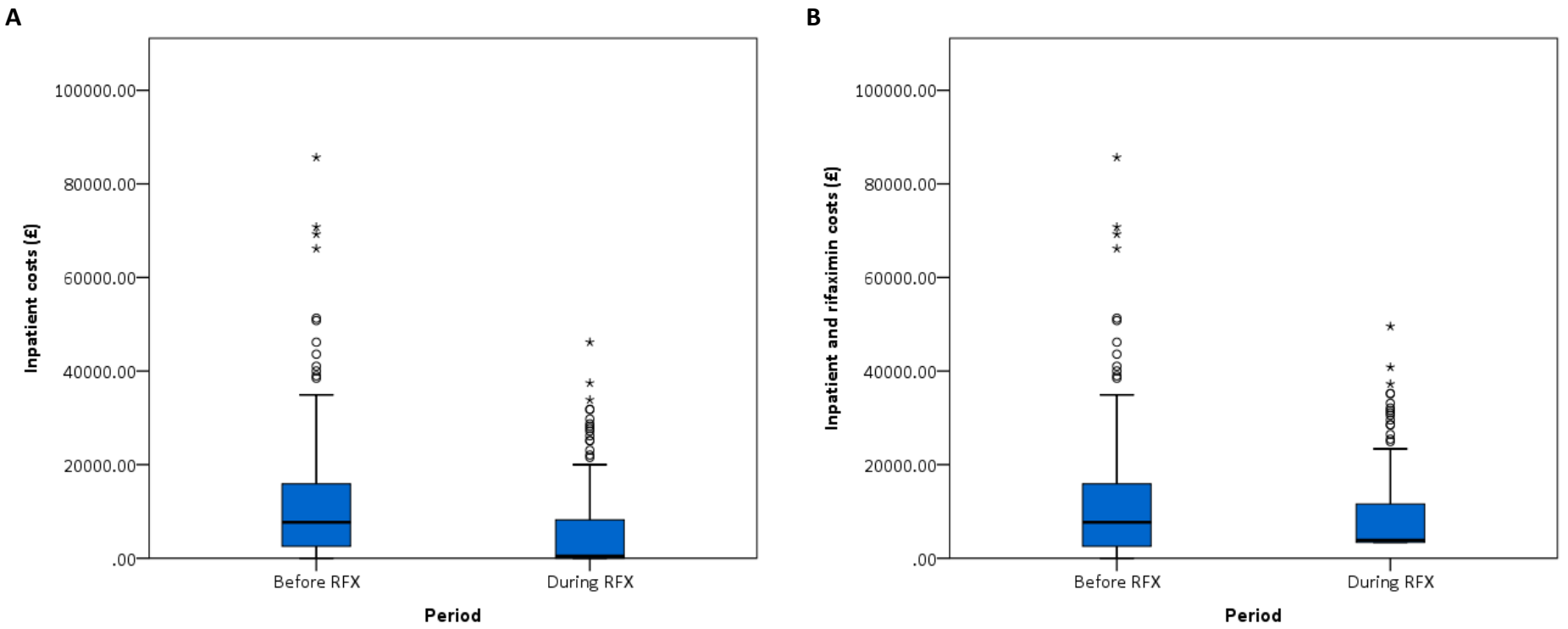


Figure 3 | Box plot showing annual emergency admission costs before and during rifaximin (A, admissions only; B, admissions and drug acquisition).



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